DETOXIFICATION CONSIDERATIONS IN THE MEDICAL MANAGEMENT OF SUBSTANCE ABUSE IN PREGNANCY*

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PHARMACOLOGY

METHADONE WAS FIRST synthesized in Germany during World War II when the usual sources of opium were blocked. Methadone has many pharmacologic properties similar to morphine. Cross-tolerance and cross-physical dependence can occur between methadone, heroin, and morphine. Methadone, like morphine, is rapidly absorbed into the bloodstream and concentrates in the liver, lungs, spleen, and kidney, with minimal amounts reaching the brain. Its action lasts from 24 to 36 hours. Withdrawal or abstinence symptoms generally appear between eight and 48 hours after the last dose and peak in approximately six days. Symptoms of withdrawal generally subside after approximately two weeks, but may continue as long as six to seven weeks. In comparison, withdrawal symptoms for heroin appear roughly four to six hours after the last dose, peak between two and three days, and subside in four to 10 days. Some investigators have indicated that the morphine abstinence syndrome may last up to six months. Because methadone is effective orally, acts longer, and has the cross-tolerance and physical dependence of other narcotic analgesics, it became the ideal candidate for "maintenance treatment" of addicts.

METHADONE MAINTENANCE

In 1965 Drs. Vincent Dole and Marie Nyswander of the Rockefeller Institute published a preliminary report of their work on "maintenance treat-

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ment.'' They sought to answer ''whether a narcotic medicine, prescribed by physicians as part of a treatment program, could help in the return of addict patients to normal society.''[1] They presented their findings as a ''progress report'' of the treatment of 22 patients for periods of one to 15 months. All patients had failed prior withdrawal treatment. The program was divided into three phases. In phase 1 addicted patients were stabilized with methadone hydrochloride as inpatients. They were stabilized at dosage levels between 50 to 150 mg/day, where the patient was neither euphoric nor sick from abstinence. They received full psychiatric, medical, and social evaluations, and classes toward a high school equivalency certificate. This phase lasted 6 weeks. In phase two the subjects became outpatients and pursued jobs, housing, and education. Phase three was the goal of treatment, in which the patients become socially normal and self-supporting. They reported two use ful effects of methadone: relief of narcotic hunger and blockade of the euphoria of diacetylmorphine.

NEONATAL ABSTINENCE

Based on this early work of Dole and Nyswander, high dose blockade methadone maintenance became the mode of therapy for most addicts, including pregnant women. In 1972 Rajegowda and Glass at Harlem Hospital were among the first to report the effect of methadone on the fetus and neonate. They compared the withdrawal symptoms of newborn infants of mothers receiving methadone maintenance therapy with newborns whose mothers were untreated heroin addicts.[3] Pregnant addicts under treatment had received a daily dose of methadone of 80 to 160 mg orally for at least one month prior to delivery. Untreated addicts had used 20 to 300 mg of heroin daily. They found this high dosage of maternal methadone associated with a higher incidence and more prolonged duration of withdrawal symptoms than was observed in infants of untreated heroin addicts.

In 1976 Ostrea, in Detroit, reported a prospective study examining factors that might influence the severity of neonatal narcotic withdrawal.[4] He found that the severity of the withdrawal did not correlate with the infant's gestational age, sex, race, or Apgar score, nor to maternal age, parity, duration of heroin intake, or the level of morphine measured in the infant's urine or blood. However, a significant number of infants suffered moderate-to-severe withdrawal if the mother was taking more than 20 mg of methadone per day. He recommended at that time that mothers getting methadone treatment be placed on a low dose regimen (<20 mg/day) at least a month before delivery to prevent serious neonatal withdrawal.

In 1977 Madden, in Chicago, reported his assessment of factors that influence the severity of withdrawal.[5] He found that 17.9% of infants whose mothers received less than 20 mg of methadone daily required treatment for withdrawal symptoms, whereas 62.5% of infants whose mothers were receiving more than 20 mg of methadone daily did. He concluded that reduction of methadone late in pregnancy reduced incidence of withdrawal symptoms among infants.

In 1977 Harper, in Long Island, published her study of the relationship between the quantity of methadone ingested by the pregnant mother, the quantity of methadone in maternal and neonatal body fluids, and subsequent neonatal withdrawal.[6] Severity of withdrawal was classified by her method published earlier.[7] She found that the severity of the withdrawal symptoms was positively correlated with the total dose of methadone taken by the mother during the last 12 weeks of pregnancy, the maternal daily dose of methadone at the time of delivery, and the intrapartum maternal serum methadone level. Neither the cord blood nor neonatal urine methadone levels correlated with either the severity of withdrawal or the time of onset of symptoms. She concluded that adequate prenatal care coupled with a decrease in methadone dosage during pregnancy was optimal management for pregnant methadone-maintained women.

In 1976 Kandall, in the Bronx, looked at birthweight patterns of infants born to populations of women with varying drug histories.[8] He found a direct effect of maternal methadone dosage in the first trimester on birthweight—the higher the dosage the larger the baby. He concluded that control of the methadone dosage in the first trimester may affect fetal growth and is of direct importance in management of the addict's pregnancy.

From 1965 through 1977 pregnant addicts were initially given high blockade dosage of methadone throughout pregnancy. Subsequently, low dose maintenance was recommended for the third trimester after recognizing that the severity of the neonatal abstinence syndrome was directly related to high (>20 mg/day) maternal methadone doses. In addition, a beneficial effect of high methadone doses in the 1st trimester was established.

MATERNAL DISPOSITION

In a report published in 1979 Mary Jeanne Kreek of the Rockefeller University prospectively studied the disposition of methadone in one woman in chronic methadone treatment throughout pregnancy.[9] Methadone dosage was maintained at 60 mg/day throughout gestation. She noted a progressive lowering of plasma levels of methadone during late pregnancy. She concluded

that lowering of levels might be due to either an increased fluid space, increased tissue reservoirs for binding methadone, or altered drug metabolism in late pregnancy. She further underscored the importance of this finding, since even mild abstinence symptoms during late pregnancy might predispose the maintained patient to polydrug or uncontrolled methadone use.

Measurable amounts of methadone were found in the amniotic fluid but without evidence of significant accumulation. Quantities of methadone in breast milk were very small, with a range of milk to plasma concentrations of 0.05 to 1.2. Based only on peak breast milk concentration of methadone (0.12 mg/ml) she calculated that not more than 60 μg would be transferred to an infant over a 24-hour period during the first month of life, and not more than 100 μg per day during the third month of life. These represent very small amounts probably with no significant pharmacologic effects.

DETOXIFICATION

In 1969 George Blinick and Robert Wallach, New York, reported results of their detoxification program for pregnant addicts.[10] They originally enrolled 300 pregnant addicts, 200 of whom delivered elsewhere. Their sample included cases with multiple admissions for detoxification and many who returned to heroin prior to labor. In fact, they state that very few of their patients remained drug free after detoxification, 40% were taking heroin prior to labor, and 10% admitted to a "fix" for self-medication of labor pains immediately prior to admission. Of the poor outcomes, the only stillborn weighed 908 grams and delivered at 24 weeks gestation. One infant weighed 936 grams, delivered after 72 hours of ruptured membranes with an Apgar of 1, and died at 26 hours with hyaline membrane disease. Another infant had a birth weight of 1,816 grams, an Apgar of 10, and died of respiratory distress syndrome. Thus, their extrapolated neonatal death rate was 20/1,000 live births, and a stillborn rate of 10/1,000 live births (12–16/1,000 general population). In light of the fact that all of the patients had been detoxified under controlled conditions at some points during their pregnancies, their fetuses were still subjected to the intermittent highs and lows of the street addict, with episodes of acute withdrawal as well as narcotic overdosages and the other myriad stresses of the street addict. In spite of this, they had a surprisingly low rate of adverse outcomes.

Subsequent to this, Rementeria in the Bronx reported a stillbirth secondary to heroin withdrawal, reviewed the literature, and suggested an etiology for the fetal death.[11] At the time the mother is withdrawing, so is the fetus. Increased fetal movements reported at this time may represent in utero sei-

zures. As a result of the stress, the fetus passes meconium and initiates strong respiratory movements, leading to in utero meconium aspiration. In addition, should labor coincide with withdrawal symptoms, the increased oxygen needed by the withdrawing fetus would occur at a time of variable uterine blood flow, resulting in fetal hypoxia, asphyxia, and death. He concluded that, given the high percentage of mothers who detoxify and revert back to heroin use, it would be wiser to encourage methadone programs to "maintain" rather than to "withdraw" addicts during pregnancy.

In 1978 the Food and Drug Administration stated that pregnant methadone-treated patients should be withdrawn within 21 days of acceptance into a program. After a fetal death occurred in his institution, Zuspan in Chicago investigated the neuroendocrine milieu of the fetus during gradual detoxification.[12] The patient studied began detoxification at 22 weeks gestational age on a dose of 20 mg of methadone per day. Her dose was decreased 2–5 mg every 6–16 days. Serial amniocenteses were performed to monitor the nor epinephrine and epinephrine response of the fetus to such a program on the premise that alterations from normal amniotic fluid epinephrine and neurepinephrine levels indicated changes in fetal homeostatis. In the one patient studied, decreasing methadone dosage was associated with increasing amniotic fluid epinephrine and neurepinephrine levels which subsequently returned to baseline when the methadone dosage was increased. The patient went on to deliver at 39 weeks a live female infant weighing 2,525 grams with mild symptoms of withdrawal. Zuspan recommended that pregnant patients not be detoxified during pregnancy, especially during the last trimester, unless a scientific means is available to monitor fetal homeostasis. The current standard of practice is to maintain a woman on the dose of methadone she is on at the time she presents to her obstetrician. As Dr. Kreek found, some women do require increasing dosage as the pregnancy progresses because of the increasing volume of distribution. Detoxification during pregnancy is, in fact, contraindicated. During the 15 years since publication of Zuspan's paper the field of obstetrics has gone from biochemical methods of fetal surveillance (urinary estriols) to electronic, ultrasound, and doppler methods utilizing nonstress tests and biophysical profiles. Surely it is time to look at fetal response to slow controlled detoxification with the aid of our newer, high-tech methods of fetal surveillance since no one has addressed this issue in 15 years.

There is scant literature on alcohol and cocaine detoxification during pregnancy. In fact, most literature on alcohol in pregnancy addresses only fetal effects. There is very little discussion or research into alcoholic treatment for

pregnant women. One author recommends that if a woman consumes more than one liter of alcohol daily, she should be hospitalized with gradual reduction of her alcohol intake. Because of the effects on the mother and the fetus and the risk of withdrawal syndromes in both mother and neonate, controlled detoxification during pregnancy is recommended. This process may require hospitalization. Disulfiram (Antabuse) should not be used during pregnancy. Sedation with hydroxyzine or a benzodiazepine may help to forestall full-blown delirium tremens.[13] However, the use of benzodiazipines during pregnancy poses the risk of teratogenesis. Phenobarbitol is presently the drug of choice for alcohol detoxification during pregnancy. However, acupuncture, long used in China for treatment of opiate withdrawal, is being utilized successfully for both alcohol and cocaine detoxification.

Although acupuncture is an ancient method of producing analgesia its mechanism of action is uncertain. H.L. Wen in Hong Kong has written several articles on auricular electroacupuncture producing subjective improvements in the clinical features of withdrawal in many heroin addicts. Vicky Clement-Jones, at St. Bartholomew's Hospital in London, studied the levels of B-endorphin, met-enkephalin, B-lipotrophin, and corticotropin in plasma and cerebrospinal fluid of heroin addicts showing features of withdrawal and during their successful treatment with electroacupuncture.[14] She showed that heroin addicts with features of heroin withdrawal had increased basal levels of B-endorphin in both blood and cerebrospinal fluid. This did not change during electroacupuncture, although this therapy suppressed the clinical features of withdrawal. Met-enkephalin levels (depressed in the heroin addict) were not elevated in blood or cerebrospinal fluid during withdrawal. However, successful electroacupuncture was associated with a rise in cerebrospinal fluid met-enkephalin levels in all patients studied (12 male patients aged 23 to 51), although concentrations in the blood did not change. This represents the first *in vivo* evidence that met-enkephalin may be involved in the physiologic basis of effective electroacupuncture. Acupuncture is successfully used for alcohol detoxification, and clients express less need for alcohol, fewer drinking episodes, and fewer admissions to detoxification centers.[15] This experience presently is being duplicated among pregnant crack addicts.

In their follow-up article 10 years later, Dole and Nyswander acknowledged that although thousands of former heroin addicts had been rehabilitated, the great majority of heroin addicts remained on the streets. In analyzing the strengths and weaknesses of methadone maintenance programs they concluded: "Methadone and other medications can be produced in large

quantity, but the compassion and skillful counseling needed for rehabilitation of addicts are not replicated in the climate of bureaucracy. As in other areas of medical practice, the question is not how many "treatment slots" are available (to use the federal terminology) but what quality of treatment the patients receive. Bureaucratic control of methadone programs has given us "slots," a rule book, and an army of inspectors, but relatively little rehabilitation. Law enforcement agencies, both police and regulatory, should reexamine the assumptions that underlie their activities. If the supply of illicit narcotics could have been eliminated by enforcement, there would be no addiction today, and if governmental regulation could have led to better treatment most of the addicts would now be off the streets."[2]

REFERENCES

1. Dole, V.P. and Nyswander, M.: A medical treatment for Diacetylmorphine (Heroin) addiction. *J.A.M.A. 193*:80–84, 1965.
2. Dole, V.P. and Nyswander, M.: Methadone maintenance treatment, a ten year perspective. *J.A.M.A. 253*:2117–19, 1976.
3. Rajegowda, B.K., Glass, L., Evans, H.E., et al.: Methadone withdrawal in newborn infants. *J. Pediatr. 81*:532–34, 1972.
4. Ostrea, E.M., Chavez, C.J., and Strauss, M.E.: A study of factors that influence the severity of neonatal narcotic withdrawal. *J. Pediatr. 88*:642–45, 1976.
5. Madden, J.D., Chappel, J.N., Zuspan, F., et al.: Observation and treatment of neonatal narcotic withdrawal. *Am. J. Obstet. Gynecol. 127*:199–201, 1977.
6. Harper, R.G., Solish, G., Feingold, E., et al.: Maternal ingested methadone, body fluid methadone, and the neonatal withdrawal syndrome. *Am. J. Obstet. Gynecol. 129*:417–24, 1977.
7. Harper, R.G., Solish, G.I., Purrow, H.M., et al.: The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. *Pediatrics 54*:300, 1974.
8. Kandall, S.R., Albin, S., Lowinson, J., et al.: Differential effects of maternal heroin and methadone use on birthweight. *Pediatrics 58*:681–85, 1976.
9. Kreek, M.J.: Methadone disposition during the perinatal period in humans. *Pharmacol. Biochem. Behav. 11*:7–13, 1979.
10. Blinick, G., Wallach, R.C., and Jerez, E.: Pregnancy in narcotics addicts treated by medical withdrawal. *Am. J. Obstet. Gynecol. 105*:997–1003, 1969.
11. Rementeria, J.L. and Nemesio, N.N.: Narcotic withdrawal in pregnancy: still birth incidence with a case report. *Am. J. Obstet. Gynecol. 116*:1152–56, 1973.
12. Zuspan, F.P., Gumpel, J.A., Mejia-Zelaya, et al.: Fetal stress from methadone withdrawal. *Am. J. Obstet. Gynecol. 122*:43–46, 1975.
13. Burrow, G.N. and Ferris, T.F.: *Medical Complications During Pregnancy,* 2nd ed. Philadelphia, Saunders, 1982, p. 541.
14. Clement-Jones, V., McLoughlin, L., Lowry, P.J., et al.: Acupuncture in heroin addicts: changes in met-enkephalin and B-endorphin in blood and cerebrospinal fluid. *Lancet 2*:380–83, 1979.
15. Bullock, M.L., Umen, A.J., Culliton, P.D., and Olander, R.T.: Acupuncture treatment of alcoholic recidivism: a pilot study. *Alcohol. Clin. Exp. Res. 11*:292–95.